



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 34292-01; Dow Corning 5700 Antimicrobial Agent; 6(a)(2) Adverse Data Submission; Review of Subchronic Inhalation Toxicity Study on Impurity Found in 5 Dow Corning Antimicrobial Agents, All Containing 3-(Trimethoxysilyl)propyldimethyloctadecyl Ammonium Chloride as the Active Ingredient; Risk Assessment for Impurity

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Tox. Chem. No. 892B
P.C. Code No. 107401
MRID No. 425118-01

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IMPORTANT NOTE: This memorandum may contain Confidential Business Information (CBI) since an impurity in several Dow Corning products is identified in this action.

I. ACTION REQUESTED

- A. Review and comment on 6(a)(2) submission from Dow Corning Corporation, dated September 23, 1992, containing a subchronic inhalation toxicity study on rats using [REDACTED] as the test material (MRID No. [REDACTED])



425118-01). [REDACTED] is an impurity, occurring at [REDACTED] in 5 Dow Corning antimicrobial products, all of which contain 3-(trimethoxysilyl)propyl-dimethyloctadecyl ammonium chloride as the active ingredient.

- B. Based on results from the subchronic inhalation study and available exposure data, perform a risk assessment, if appropriate, for persons exposed to [REDACTED]

II. CONCLUSIONS/RECOMMENDATIONS

- A. The submitted subchronic inhalation study was reviewed. In addition to treatment-related organ weight changes and histopathology in the adrenals, liver and kidneys of males and in the adrenals of females, epithelial hyperplasia of the urinary bladder (a potential pre-neoplastic lesion) was consistently observed in both males and females. There was no NOEL for this effect in females. In addition, a micronucleus assay on bone marrow cells, performed at termination of the study, was positive for females at the highest exposure level tested. A DER for this study is included in this memorandum.
- B. Based on epithelial hyperplasia of the urinary bladder observed in the above study, a risk assessment for persons directly exposed to [REDACTED] was performed. It was determined that the only persons directly exposed to this chemical per se would be certified commercial applicators (mixer/loaders) diluting the antimicrobial products with water (or other organic solvents) during manufacturing applications. Since [REDACTED] reacts with water to form a different chemical compound (see below), exposures of other persons to aqueous solutions of this chemical were not considered to be of concern at this time. In addition, persons exposed to bonded coatings of this antimicrobial agent on treated materials (see below) also were not considered to be of concern at this time. At the request of TB-1, OREB provided an exposure estimate for mixer/loaders (M/Ls) directly exposed to [REDACTED] (see memorandum by Winston Dang, dated February 9, 1994, copy attached).
- C. A risk assessment for M/Ls directly exposed to [REDACTED] as a result of handling the Dow Corning antimicrobial products, was performed. The Margin of Exposure (MOE) for [REDACTED] (containing [REDACTED] as an impurity) was calculated to be 2.5.

- D. Toxicology Branch I considers the MOE of 2.5 calculated above to be inadequate for M/L handling products containing [REDACTED] and recommends that the registrant (Dow Corning Corporation) be required to submit additional data/information which would permit calculation of a substantially higher MOE (equal to or above 100), and/or take appropriate steps to significantly reduce the exposure of M/L to [REDACTED]. For further details, see "RISK MITIGATION" on pages 8 and 9 of this memorandum.

III. BACKGROUND

- A. [REDACTED] has been identified by Dow Corning Corporation as being an impurity [REDACTED] occurring at concentrations of [REDACTED] in 5 of their antimicrobial products, all of which contain 3-(trimethoxysilyl)propyldimethyloctadecyl ammonium chloride, a silicone quaternary ammonium salt, as the active ingredient. These 5 antimicrobial products are:

- 1) Dow Corning 5700 Antimicrobial Agent
(EPA Reg. No. 34292-1)
- 2) Dow Corning 5772 Antimicrobial Agent
(EPA Reg. No. 34292-2)
- 3) Sylgard Antimicrobial Treatment
(EPA Reg. No. 34292-3)
- 4) Dow Corning 5700 Antimicrobial Agent for Manufacturing
(EPA Reg. No. 34292-5)
- 5) Dow Corning 5772 Antimicrobial Agent for Manufacturing
(EPA Reg. No. 34292-6)

A copy of the label and accompanying Technical Bulletin for Dow Corning 5700 Antimicrobial Agent is attached to this memorandum. As described in the Technical Bulletin, these antimicrobial products are used in numerous manufacturing applications to form durable, bonded coatings on the surfaces of a wide variety of substrates and materials, including many with considerable potential exposure to humans, (e.g. diapers, underwear, outerwear apparel, bedsheets, etc.). The bonded coatings offer broad spectrum, antimicrobial protection and are leach-resistant, nonmigrating and not consumed by microorganisms.

- B. The Dow Corning antimicrobial products are incorporated during the manufacturing process directly into formulations to make end-use products (e.g. into polyurethane foam formulations) or are diluted with water (or other organic

solvents) and then applied to substrates to give a 0.1-1.0% W/W of the active ingredient. The substrates are then dried to effect condensation of silanol groups (i.e. polymerization and bonding) and to remove the water.

- C. When the active ingredient in the antimicrobial products, 3-(trimethoxysilyl)propyldimethyloctadecyl ammonium chloride and the impurity, [REDACTED] come into contact with water, a hydrolysis reaction occurs which converts the methoxy groups in both chemicals to their "hydroxy" forms, 3-(hydroxysilyl)propyloctadecyldimethyl ammonium chloride and [REDACTED] respectively. Therefore, the only direct exposures to the methoxy impurity per se are to M/Ls who dilute the antimicrobial products in water (or other organic solvents) prior to or during the manufacturing process itself. Persons exposed to the bonded hydroxy form of the impurity in final end-use products would not be directly exposed to the methoxy impurity in the antimicrobial agents (verbal communication from Mike Hales, Dow Corning Corporation, on February 2, 1993).
- D. Dow Corning Corporation, on its own initiative, performed a 28-day subchronic inhalation toxicity study on rats using the impurity, [REDACTED] as the test material. Based on preliminary results in this study, Dow Corning submitted two earlier 6(a)(2) notifications to EPA as follows:
- 1) notification dated February 13, 1992 in which preliminary data obtained in the bone marrow micronucleus assay portion of the study was presented (MRID No. 422042-01), and
 - 2) notification dated May 15, 1992, in which preliminary data from the histopathologic examination conducted as part of the same study was presented (MRID No. 423341-01).

The present submission, dated September 23, 1992, is a 6(a)(2) follow-up submission to the earlier notifications which presents the final full report of the subchronic inhalation toxicity study (MRID No. 425118-01).

IV. REVIEW OF THE SUBCHRONIC INHALATION TOXICITY STUDY

The Executive Summary for the subchronic inhalation toxicity study is presented below. The DER for this study is included in this memorandum.

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study (MRID No. 425118-01), groups of 10 male and 10 female CD rats were exposed to vapors of [REDACTED]

This study is classified as Core Supplementary because the 28-day duration of this study is less than the 90-day duration required in the Subdivision F Guidelines for a subchronic inhalation study (82-4). This study, therefore,

can not be upgraded. In addition, no NOEL was established in this study.

Although this study is not acceptable as a Subdivision F Guidelines study, it nevertheless does contain valid information that indicates a toxicological effect of concern in the urinary bladder of female rats at 10 ppm and in both male and female rats at higher exposure levels (simple epithelial hyperplasia).

V. RISK ASSESSMENT (MOE) FOR [REDACTED]

A. NOEL for Toxicological End-Point of Concern

In the 28-day subchronic inhalation toxicity study on rats using [REDACTED] as the test material (MRID No. 425118-01), treatment-related epithelial hyperplasia of the urinary bladder (a potential pre-neoplastic lesion) was observed in male rats at ≥ 50 ppm and in female rats at ≥ 10 ppm. The incidence of this lesion was 0/10, 0/10, 1/10, 5/10 and 10/10 for males and 0/10, 2/10, 2/10, 2/10 and 9/10 for females at exposure levels of 0 (control), 10, 50, 100 and 200 ppm, respectively. Although a NOEL of 10 ppm was established for this effect in males, no NOEL was established in females since the lesion was observed in 2/10 females at 10 ppm, the lowest exposure level tested. The flat dose-response curve for females from 10 to 100 ppm (2/10 responses at each of 3 exposure levels tested) and the rather steep dose-response curve for males, however, suggest that the true NOEL for this effect in females may be only slightly less than 10 ppm. Therefore, an additional uncertainty factor of 10 was used to approximate the NOEL for females in this study. For the purposes of this risk assessment, it will be assumed that the NOEL for females is $10 \text{ ppm} / 10 = 1 \text{ ppm}$.

The actual daily exposure of female rats to 1 ppm [REDACTED] in units of ug/kg/day, was calculated as follows.

[REDACTED]

[REDACTED]

NOEL (female rats) = 2,160 ug/kg/day (assuming 100% absorption via inhalation route of exposure)

B. Exposure Estimate for Mixer/Loaders

The direct exposure of mixer/loaders (M/L) to [REDACTED] [REDACTED] was estimated in a memorandum, dated February 9 1994, from Winston Dang (OREB) to Karen Hamernik (TB-I) (copy attached). [REDACTED]

[REDACTED]

Actual Daily Exposure (M/L) = 857.06 ug/kg/day

Absorbed Dose (M/L) = 857.06 ug/kg/day (assuming 100% absorption via dermal* and inhalation routes of exposure)

* Since no dermal absorption study is available for [REDACTED] [REDACTED] 100% absorption was assumed.

C. Calculation of Margin of Exposure (MOE)

The Margin of Exposure (MOE) was calculated as follows.

MOE = NOEL (female rats) / Absorbed Dose (M/L)

= 2,160 ug/kg/day / 857.06 ug/kg/day = 2.5

The MOE for [REDACTED] (containing [REDACTED] as an impurity) was calculated to be 2.5.

VI. RISK MITIGATION

- A. Toxicology Branch I considers the MOE of 2.5 calculated above to be inadequate for M/L handling products containing [REDACTED] and recommends that the registrant (Dow Corning Corporation) be required to submit additional data/information which would permit calculation of a substantially higher MOE (equal to or above 100), and/or take appropriate steps to significantly reduce the exposure of M/L to [REDACTED]
- B. Regarding the submission of additional data/information, consideration should be given to performing a new exposure study for [REDACTED] in which dermal and inhalation components would be separately determined. The test material for this study should be the registered product per se (e.g. Dow Corning DC 5700 Antimicrobial Agent, EPA Reg. No. 34292-1) which contains the "methoxy" form of the impurity. It is recommended that OREB be consulted prior to conducting such a study. Accompanying this exposure study should be either a 90-day subchronic dermal toxicity study (Guideline 82-3) or a dermal penetration study (Guideline 85-3) in order that the dermal component of the exposure might also be considered and related to a relevant toxicological endpoint. The test material in these latter studies should be [REDACTED] [It should be noted that the previously submitted 90-day subchronic dermal toxicity study on rats using DC 5700 hydrolysate as the test material (Dow Corning Corp., study 3933-19, 12/18/89) would not be satisfactory for this purpose.]
- C. Regarding steps to reduce the exposure of M/L to [REDACTED] the following should be considered.
- 1) With respect to the use of personal protective equipment, it should be noted that the label requirement to wear gloves, which is already on the

label for DC5700 Antimicrobial Agent (EPA Reg. No. 34292-1) and presumably on the labels for the other Dow Corning antimicrobial products as well, would not alter the MOE calculated above because the M/L in the "CMA Study" also wore gloves in 14 of the 16 studies considered. Further, since the inhalation component of the exposure to M/L in the "CMA Study" was relatively small (verbal communication with Winston Dang of OREB), a new requirement on the labels to use respirators probably would not reduce the exposure appreciably.

- 2) Use of engineering controls, particularly a closed system for diluting the products, would reduce the exposure to M/L.